Sexually Transmitted Diseases, March 2006, Vol. 33, No. 3, p.151–155
DOI: 10.1097/01.olq.0000204506.06551.5f

Syphilis Treatment and HIV Infection in a Population-Based Study of Persons at High Risk for Sexually Transmitted Disease/HIV Infection in Lima, Peru

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Objectives: **The objective of this study was to characterize syphilis epidemiology and the relationship of HIV status and initial rapid plasma reagin (RPR) titer to syphilis treatment in Lima, Peru.**

Study Design: **We screened 1,261 individuals at high risk for sexually transmitted diseases for syphilis and HIV infection. Syphilis was treated with penicillin injection or doxycycline; treatment was repeated in unresponsive cases.**

Results: **The prevalence of syphilis was 7.7%, 1-year incidence rate was 4.7%, and reinfection rate was 42.7%. The treatment success rate was 93.4% (71 of 76); those with initial RPR titers ≤1:8 were less often treated successfully (86.8% vs. 100%, $P = 0.054$) and required additional treatment more often (26.2% vs. 7.7%, $P = 0.028$) than those ≥1:16. HIV infection was associated with syphilis, prevalent in 15.6% and 3.7% of those with and without syphilis, respectively ($P < 0.001$), but did not affect treatment success (90.9% vs. 93.8%).**

Conclusions: **Syphilis was common, associated with HIV infection, and less responsive to therapy in those with initial RPR titers ≤1:8. HIV infection did not affect syphilis treatment success rates.**

INFECTION WITH OTHER SEXUALLY transmitted diseases (STDs) has been shown to increase the risk of HIV transmission.[1–3] This association is particularly apparent among ulcerative infections such as herpes simplex virus type 2, chancroid, and syphilis, in which HIV transmission is increased two to five times secondary to increased viral shedding and facilitated virus entry.[4,5] Improved STD management is efficacious in reducing HIV transmission in certain populations.[6]

This study was funded by the NIMH Collaborative HIV/STD Prevention Trial, grant no. U10 MH61536 (Thomas J. Coates, PhD, PI).

Presented at the 7th Annual Bay Area International Health Conference, San Francisco, California, April 2, 2005.

The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

This study was funded by the NIMH Collaborative HIV/STD Prevention Trial, grant no. U10 MH61536 (Thomas J. Coates, PhD, PI), and partially supported by LP-CRADA NM-04-1787 and Work Unit 847705 82000 25GB B0016.

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Received for publication April 18, 2005, and accepted July 21, 2005.

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Primary syphilis, the result of infection with the spirochete *Treponema pallidum*, typically results in a painless ulcer at the site of infection approximately 3 weeks after exposure.[7] If untreated, systemic spread may lead to the development of secondary syphilis, which associated with fever, lymphadenopathy, and diffuse rash. Symptoms often resolve spontaneously despite continued presence and replication of the organism with occasional relapses up to 5 years later.[8] Latent syphilis, the persistence of positive serology tests without symptoms, may be divided into early and late, with early–latent syphilis delineated as infection within the past year and late–latent as infection of greater than a year (or unknown) duration. Tertiary syphilis, with a lifetime incidence of approximately 25% among those not treated at an earlier stage, encompasses the major complications of untreated infection and is manifest most commonly as neurosyphilis, cardiovascular syphilis, or gummatous syphilis.[8] Syphilis infection in pregnant women carries the additional danger of congenital syphilis.[7]

The treatment of syphilis remains part science and part professional habit. Despite being the treatment of choice for decades, penicillin remains extremely active against *T. pallidum*. Although not backed by major comparison studies on dosages or regimens, the Centers for Disease Control and Prevention (CDC) recommends a single-dose, 2.4-million unit (MU) penicillin benzathine G intramuscular injection or 2 weeks of a tetracycline for early syphilis and three consecutive weekly penicillin injections for late–latent and tertiary syphilis. Internationally, there does not exist a treatment consensus, because regimens and medications vary by region.[9] Treatment is judged to be successful with at least a fourfold decline in nontreponemal antibody titer in 6 to 12 months with early syphilis and 12 to 24 months in late syphilis.[7] A recent pilot study examining the efficacy of azithromycin for the treatment of early syphilis demonstrated cure rates for a single benzathine penicillin injection of 86% and 100% at 3 and 9 months, respectively, compared with 88% and 100% for 2 g single-dose oral azithromycin.[10]

Syphilis rates in South America differ by country and population,[11–16] from 28% among female sex workers in urban Guyana[17] and 13% among female sex workers in Buenos Aires,[18] to 3% among pregnant women in Brazil[19] and 1% among blood donors in Ecuador, Chile, and Venezuela.[20]

Likewise, estimates of syphilis prevalence in Peru vary widely: 1.0% among blood donors,[21] 1.7% among young job applicants and students,[22] 3.2% among unregistered prostitutes,[23] 16.0% among men who have sex with men (MSM),[24] and 18% among HIV-positive men.[25] Although total visits to private clinics for syphilis have not appreciably increased for the past 15 years,[26] the number of reported cases of congenital syphilis increased from 266 to 629 between 1999 and 2000.[21]

The rate of HIV infection in Peru among the general population is 0.2%,[21] but rates as high as 18.5% have been found in populations of MSM.[24] Because 95% of all HIV infections in Peru are transmitted sexually,[21] understanding the prevalence of syphilis and its facultative relationship with HIV infection is important. As such, syphilis remains a substantial public health problem in Peru, particularly among high-risk populations, underscoring the need for effective surveillance and treatment.

As part of a large, community-based, multinational STD/HIV prevention trial, we explored the relationship of treatment modality, HIV status, and initial nontreponemal antibody titer to serologic response to syphilis treatment.

Materials and Methods

Study Design and Subjects

The National Institute of Mental Health Collaborative HIV/STD Prevention Trial was a cohort study conducted in three large cities in Peru among men and women aged 18 to 40 years. Each city was made up of a number of sites based on their respective populations: Lima (20 sites), Chiclayo (6), and Trujillo (4).

Recruitment was conducted (May–July 2003) in microvenues of low-income neighborhoods such as bars, pool halls, soccer fields, and street corners where men and women, who were part of the target population at high risk for HIV and STDs, congregate. Study recruiters screened potential participants among patrons at the microvenues and surroundings. To qualify for the study, participants aged 18 to 40 years had to live in the neighborhood and frequent the microvenues at least twice a week. One of every three individuals who qualified was asked to participate; an appointment was made for an interview and specimen collection of willing participants. The sample size was 50 participants from each of the 30 venues.

Data Collection

Temporary offices were established in each of the venues to accommodate study participants who were assigned study appointments. After signing the informed consent document, participants were interviewed, submitted blood samples for biologic testing, underwent assessment for current STD symptoms, and received counseling and educational materials related to STDs. All participants were given 25 soles (approximately $7 U.S.) for their participation.

Approximately 15 mL of venous blood was collected for testing for HIV infection, syphilis, and herpes simplex virus type 2. Participants testing positive for syphilis were asked to return 4, 8, and 12 months later to monitor treatment efficacy through serial rapid plasma reagin (RPR) nontreponemal antibody titer measurements.

Laboratory Testing

All laboratory specimens were transported to the U.S. Naval Medical Research Center Detachment in Lima, Peru, for testing, a laboratory site dedicated to biologic testing affiliated with U.S. and approved Peruvian academic institutions. All protocols strictly adhered to U.S. Navy standards for quality control and personnel training, and testing kits were used according to the manufacturers' specifications. Genetic Systems HIV-1/HIV-2 Peptide EIA (Bio-Rad, Hercules, CA) was used to screen for the presence of antibodies to HIV subtype 1 and 2 with positive samples confirmed by Western blot identification of HIV-1 antibodies (Genetic Systems; Bio-Rad). RPR-nosticon II rapid plasma reagin (RPR) kits (Shield Diagnostics, Dundee, U.K.) were used to screen for *T. pallidum* with reactive titers confirmed by Serodia-TPPA (Fujirebio Diagnostics Inc., Toyko, Japan) and deemed positive for syphilis if reactive. Test results were double-checked and nondiagnostic assays were repeated. All laboratory data were sent to the Research Triangle Institute (Research Triangle Park, NC) for data security, verification, blinding, and summation.

Treatment, Cure, and Reinfection

Participants with reactive *Treponema pallidum* particle agglutination (TPPA) tests were referred for treatment and encouraged to bring in or refer sexual partners for treatment at any time and at the study's expense. Because of confidentiality, the sexual partners of infected participants were not actively sought out or otherwise contacted unless the participant requested such service, although they were encouraged to be notified and treated in any case. We treated syphilis cases with a single 2.4-MU intramuscular injection of penicillin benzathine G or 100 mg of doxycycline by mouth twice daily for 2 weeks if participants reported a penicillin allergy or refused the injection. Those refusing or unable to give consent for treatment were offered treatment again at the 4-, 8-, and 12-month follow-up appointments. If the participant did not have a 4-fold drop in their RPR titer at the 4-, 8-, or 12-month follow ups, they were treated with a single course of weekly 2.4-MU intramuscular injections of penicillin benzathine G for 3 weeks or 100 mg of doxycycline by mouth twice daily for 4 weeks. Those with titers still not dropping adequately to be considered successfully treated after the more extensive regimen had surveillance titers drawn at successive follow-up appointments for observation but not offered further treatment.

We defined successful treatment as a fourfold decline in RPR titer from pretreatment levels or titer conversion from reactive to nonreactive at any time during the 12 months. A participant was considered to have been reinfected if the criteria for successful treatment were met, and then at the 8- or 12-month follow-up appointments, they were found to have had a fourfold RPR titer increase from its lowest level or converted from nonreactive to reactive. Treatment failure occurred if participants at no time experienced a fourfold decline in RPR titer or failed to convert a 1:4 or 1:2 titer to nonreactive despite receiving both a short and long course of antibiotics.

Data Analysis

Statistical comparisons between outcomes were made with chi-squared tests and Fisher exact test when appropriate. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All P values are two-tailed and considered significant if ≤ 0.05. Epi Info 3.01 (Centers for Disease Control and Prevention, Atlanta, GA) was used for all statistical analyses.

Results

Of the 1,261 participants screened in Lima, there were 96 cases (7.6%) of asymptomatic syphilis confirmed by TPPA, of which 76 (79.2%) completed follow up by also returning for a repeat RPR titer measurement 1 year later. Among those not available at 1-year follow-up, eight were treated with at least one course of antibiotics, two were successfully treated at 4 or 8 months, three were lost to follow up secondary to hospitalizations or death, and the remainder (7) either refused treatment or failed to return to the initial encounter for their results and treatment. Five participants (5.2%) brought partners to be treated.

After the first screening, there were 14 new cases of syphilis throughout the year, representing 1.2% (14 of 1,165) of the study population who initially tested negative for syphilis and 41 cases of reinfection (42.7% of syphilis cases) for an annual incidence of 4.7%. A total of 21.4% (3 of 14) of the new cases were participants coinfected with HIV, and new cases were associated with HIV infection (OR, 7.12; $P = 0.015$; CI, 1.23–28.18). There was no association between risk of reinfection or initial RPR titer.

The syphilis cure rate was 93.4% (71 of 76); of the five treatment failures, one had concurrent HIV infection. The cure rate among those with initial RPR titers of ≥1:16 and ≤1:8 were 100% and 86.8%, respectively ($P = 0.054$). By treatment modality, the cure rates for penicillin and doxycycline were 94.8% and 88.8%, respectively (OR, 2.29; $P = 0.59$; CI, 0.17–21.60; Table 1). Four months after the initial treatment, 17.2% (14 of 81) of participants had not been successfully treated and were given additional treatment (Table 2); this was necessary more often for those with initial RPR titers ≤1:8 than those with titers ≥1:16 (26.2% vs. 7.7%; OR, 4.26; $P = 0.028$; CI, 0.99–25.47). The additional treatment was successful for cases with titers ≥1:16 (2 of 2) but only for 30% (3 of 10) of those with titers ≤1:8 ($P = 0.15$). Although there was no significant difference in the need for additional treatment by initial treatment modality, none of the participants given 4 weeks of doxycycline were successfully treated (zero of 3), whereas 55.5% (5 of 9) of those receiving three penicillin injections were treated successfully ($P = 0.205$).

The prevalence of HIV infection in this study was 15.6% (15 of 96) among syphilis cases and 3.7% (43 of 1,165) among those without syphilis, and was strongly associated with syphilis infection (relative risk, 4.24; $P < 0.001$; CI, 2.45–7.35). Of the 15 syphilis cases with concurrent HIV infection, 11 had complete follow-up data available and 10 were successfully treated (8 of 9 penicillin, 2 of 2 doxycycline) for a rate of 90.9%, compared with 93.8% for HIV-negative participants (Table 3). Two syphilis cases, both with HIV infection, had an initial RPR titer of >1:512, the maximal quantitative dilution calculated in the laboratory; one was successfully treated and the other had a posttreatment titer of 1:256 before being hospitalized and was lost to follow up.

Four cases of syphilis occurred in women; two had initial RPR titers of 1:18 and two 1:16, none were coinfected with HIV, and all were treated successfully with penicillin, although two were reinfected.

TABLE 1. Syphilis Treatment Success Rate Percentages (n/N) by Baseline Rapid Plasma Reagin Titer and Treatment Modality

Titer	Penicillin	Doxycycline	Total
≤1:8	88 (22/25)	84.6 (11/13)	86.8 (33/38)
≥1:16	100 (33/33)	100 (5/5)	100 (38/38)
Total	94.8 (55/58)	88.8 (16/18)	93.4 (71/76)

TABLE 2. Percentage of Syphilis Cases (n/N) Requiring Additional Treatment by Baseline Rapid Plasma Reagin Titer and Primary Treatment Modality

Titer	Penicillin	Doxycycline	Total
≤1:8	23.3 (7/30)	33.3 (4/12)	26.2 (11/42)
≥1:16	8.8 (3/34)	0 (0/5)	7.7 (3/39)
Total	15.6 (10/64)	23.5 (4/17)	17.2 (14/81)

Discussion

Syphilis was common in this population and strongly associated with HIV infection, corroborating findings reported by others.[27–29] Although overall treatment success rates were high, we found that syphilis cases with an initial nontreponemal titers ≤1:8 were less often successfully treated 1 year after treatment with penicillin or doxycycline than those with titers of ≥1:16. Cases with low titers also required additional treatment more frequently secondary to lack of response to a single course of therapy. Finally, the high syphilis incidence and rate of reinfection in this high-risk population coupled with a very low rate of partner notification make adequate prevention and treatment a public health priority.

Primary, secondary, and early–latent syphilis are collectively termed early syphilis. Cases of syphilis without signs or symptoms are considered latent syphilis; differentiating early–latent and late–latent syphilis requires establishment of infection within the past year. This is an important distinction from a treatment point of view, because the current treatment recommendation for late–latent syphilis is three weekly penicillin injections compared with a single injection for early syphilis. The rationale for this difference is that the metabolism of *T. pallidum* changes over time, dividing less frequently, necessitating increased duration of antibiotic activity.[30]

The relationship of nontreponemal serologic titers such as the RPR or Venereal Disease Research Lab (VDRL) tests to syphilis progression and treatment is complex and further complicated by host immune response, autoimmune and rheumatologic diseases, previous syphilis infection, and HIV infection. The natural history of serologic titers normally dictates a gradual rise with the onset of infection, not always detectable while symptomatic, until a peak months later correlated with the onset of secondary syphilis, after which time the titers decrease throughout the host lifetime.[31] As such, low serologic titers are often correlated with late infection.

There exist several possible explanations for the difference in treatment success rates and the need for additional treatment between patients with high and low titers in this study. Because it was conducted outside of a clinical setting, physical examinations were not carried out and a reliable history of painless genital ulcers was not elicited for the purposes of syphilis stage diagnosis. Thus, by treating each participant as having early syphilis, with only a single course of penicillin or doxycycline, late–latent syphilis cases may have been undertreated. Furthermore, titers of those with latent syphilis or a history of previously treated syphilis infection are believed to decrease more slowly than those without such infection histories, potentially making 1 year an inadequate

TABLE 3. Syphilis Treatment Success Rate Percentages (n/N) by Baseline Rapid Plasma Reagin Titer and HIV Status

Titer	HIV-Positive	HIV-Negative	Total
≤1:8	75.0 (3/4)	88.2 (30/34)	86.8 (33/38)
≥1:16	100 (7/7)	100 (31/31)	100 (38/38)
Total	90.9 (10/11)	93.8 (61/65)	93.4 (71/76)

amount of time to definitively evaluate treatment response.[7,32,33] Finally, firm conclusions regarding differences in treatment modality cannot be drawn from this study, especially because, although compliance with penicillin injections was assured, the study depended on the participants to complete the appropriate courses of doxycycline at home, where the regimen was more complicated and observed therapy not feasible.

HIV infection was highly associated with the presence of syphilis in this population, and the cure rate was comparable to that of participants without HIV infection. The serologic host response to syphilis infection and treatment in HIV-positive individuals is varied with the literature offering conflicting findings. Nontreponemal antibody titers among individuals with both syphilis and HIV infection have been shown to be higher than those without HIV infection[34] and to decrease more slowly with therapy despite adequate clinical improvement.[35–37] Conversely, patients with later-stage HIV infection have shown a diminished or absent serologic response to *T.* pallidum[38,39] and a tendency to lose reactivity after efficacious treatment.[40,41] The response of treponemal tests (FTA-ABS or TPPA) in HIV-positive individuals seems to be less varied,[42] although HIV infection may account for some "false-negative assay results" in which treponemal-specific tests do not confirm infection.[43] Overall, despite potential fluctuations in serologic titers in HIV-positive populations, the clinical response of syphilis to appropriate treatment appears to be sufficient, although increased vigilance for treatment failure is necessary given the potential consequences.

This study demonstrated an extremely high rate of participant reinfection with syphilis after successful treatment, the cause of which is surely multifaceted. This population was chosen for study in part because of its relatively high risk of acquiring STDs and so some amount of reinfection from continued high-risk behavior is to be expected. Additionally, the use of any interventional or educational campaign is dependent on the ability of the target population to easily understand the problem and put realistic corrective measures into place with proper training, a property that cannot be assured in this study because, despite treatment and counseling, such points were never directly measured. Objective data does show, however, that the risk of reinfection in this study was independent of sex, HIV status, and initial RPR titer. Finally, the lack of partner treatment points to an overall deficiency of partner notification. This can be an overwhelming problem because no number or combination of medication regimens can be protective against syphilis if a regular sexual partner is infectious and does not seek treatment. We cannot be sure whether study participants understood the importance of notifying their partners, went through with the notification, or brought them for treatment elsewhere, but ongoing work in this particular area points to low overall levels of partner notification in cases of STDs, with embarrassment, multiple casual partners, and fear of breaking up endorsed most frequently as reasons for no notification (unpublished data).

A recent review of international syphilis treatment guidelines, as well as the evidence in support of such guidelines, shows that despite evaluating the same studies, the CDC and European health authorities differ in first-line recommended treatment regimens.[9] The United Kingdom, for example, treats early syphilis with daily intramuscular injections of 750 mg of procaine penicillin for 10 days as a result of concerns about benzathine penicillin failure rates, particularly among pregnant women and the immunocompromised, and its low cerebrospinal fluid penetration; benzathine penicillin is second-line and given in two 2.4-MU intramuscular injections 1 week apart.[44] Treatment of latent syphilis follows the same pattern, with the United Kingdom extending the injections of procaine penicillin to 17 days and maintaining three weekly benzathine penicillin injections as second line.[45] Official European guidelines, despite the diversity of individual national recommendations, largely conform to those of the CDC.[46]

Several areas of research in the field of syphilis management have yet to be sufficiently explored. This study raises questions related to the efficacy of a single course of penicillin or doxycycline for patients with low initial nontreponemal titers and, given the low treatment response rate, the role of doxycycline in the treatment of latent syphilis. The efficacies of alternative therapies, including single-dose azithromycin for early syphilis, are currently being explored. Finally, work is ongoing to delineate the most effective treatment regimens for special subsets of syphilis patients such as those with HIV infection or neurosyphilis.

This study was not without its limitations. Despite following participants for 1 year, some decrease in RPR titers could continue beyond this time, allowing fewer participants to have "failed" treatment. The overall number of syphilis cases in this study was high considering it was a cross-sectional community-based study, but still lacked sufficient numbers to carry out more sensitive analysis of response to the different medical therapies according to titer. As an epidemiologic undertaking, rather than a clinical one, medical histories, physical examinations, and other laboratory tests were not used to better characterize participant disease, thereby precluding definitive diagnosis of late or neurosyphilis. Finally, if such interventions are to have a real and sustainable positive impact on the study population, a better mechanism for partner notification and treatment must be considered.

Syphilis was found to be common in this high-risk population, often concurrent with HIV infection. Participants with low initial RPR titers may have been less frequently successfully treated 1 year after treatment than those with higher titers. Because lower titers often signify older infection, these findings support current CDC and U.K. guidelines for syphilis treatment, which emphasize extended treatment regimens for suspected late syphilis. The high rate of reinfection and low rate of partner treatment demonstrated by this study underscore the need for effective partner notification and treatment strategies to combat the spread of HIV and other STDs.

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